BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Drugs 1999 Jun; 57 (6): 921-930
0012-6667/99/0006-0921/$10.00/0

Rosiglitazone

Julia A. Barman Balfour and *Greg L. Plosker*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Rosiglitazone, a thiazolidinedione antidiabetic agent, improves insulin resistance, a key underlying metabolic abnormality in most patients with type 2 (non–insulin-dependent) diabetes mellitus.

▲ In animal models of insulin resistance, rosiglitazone decreased plasma glucose, insulin and triglyceride levels and also attenuated or prevented diabetic nephropathy and pancreatic islet cell degeneration.

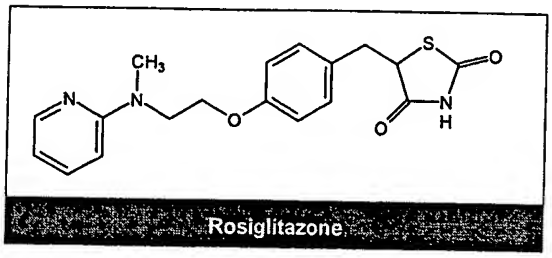
▲ In contrast with troglitazone, rosiglitazone does not induce cytochrome P4503A4 metabolism. It does not interact significantly with nifedipine, oral contraceptives, metformin, digoxin, ranitidine or acarbose.

▲ In clinical trials in patients with type 2 diabetes mellitus, rosiglitazone 2 to 12 mg/day (as a single daily dose or 2 divided daily doses) improved glycaemic control, as shown by decreases in fasting plasma glucose and glycosylated haemoglobin (HbA_{1c}).

▲ Addition of rosiglitazone 2 to 8 mg/day to existing sulphonylurea, metformin or insulin therapy achieved further reductions in fasting plasma glucose and HbA_{1c}. Oral combinations improved insulin sensitivity and β-cell function according to a homeostasis model assessment.

▲ Consistent with its mechanism of action, rosiglitazone appears to be associated with a low risk of hypoglycaemia (<2% of patients receiving monotherapy). There is no evidence to date that rosiglitazone shares the hepatotoxicity of troglitazone.

Features and properties of rosiglitazone (BRL 49653)	
Indication	
Management of type 2 diabetes mellitus	
Mechanism of action	
Thiazolidinedione antidiabetic agent	Insulin sensitiser; peroxisome proliferator activated receptor-γ agonist
Dosage and administration	
Usual dosage in clinical trials	2-8 mg/day
Route of administration	Oral
Frequency of administration	Once or twice daily
Pharmacokinetics (2mg oral dose; fasted versus fed state)	
Peak plasma concentration	152 versus 121 μg/L
Time to peak plasma concentration	1.3 versus 3.5h
Area under the plasma concentration-time curve	860 versus 805 μg/L · h
Elimination half-life	3.64 versus 3.78h
Adverse events	
Most frequent	Upper respiratory tract infection
Drug interactions	
No clinically significant interaction with rosiglitazone	Nifedipine, norethindrone, ethinylestradiol, digoxin, metformin, ranitidine, acarbose



Rosiglitazone

Rosiglitazone is a thiazolidinedione, a relatively new class of antidiabetic agents which enhance sensitivity to insulin in the liver, adipose tissue and muscle, resulting in improved insulin-mediated glucose disposal.[1] Insulin resistance is a pivotal underlying metabolic abnormality in most patients with type 2 (non–insulin-dependent) diabetes mellitus. Hypersecretion of insulin occurs until the pancreas can no longer compensate for the reduced sensitivity of the tissues to insulin and then overt type 2 diabetes results (reviewed by Henry[2] and Bloomgarden[3]).

In all animal and human studies discussed in this article, drugs were given orally unless specified otherwise. In animal studies, dosages are expressed per kg bodyweight unless specified otherwise.

1. Pharmacodynamic Profile

Mechanism of Action

The mechanism of action of rosiglitazone and other members of its class is yet to be clarified. Available data suggest that these agents can modulate several processes to increase sensitivity to insulin. These include effects on insulin receptor kinase activity, insulin receptor phosphorylation, numbers of insulin receptors and hepatic glucose metabolism.[4] However, it has been suggested that many of the glucoregulatory effects of thiazolidinediones are mediated via reduced systemic and tissue lipid availability.[5]

One key action of thiazolinidinediones is to activate the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ).[6-8] This receptor, which is expressed at high levels in mammalian adipose tissue, regulates the transcription of several genes involved in preadipocyte differentiation and insulin-mediated glucose uptake in peripheral tissues. Thiazolidinediones promote adipose cell differentiation by activating PPAR-γ. They reduce expression of leptin (a signalling factor expressed by the *ob* gene which regulates appetite, bodyweight and energy balance) and tumour necrosis factor-α (TNFα), while increasing expression of lipoprotein lipase, adipocyte lipid-binding protein (aP2) and GLUT-4 (which plays a key role in the facilitated transport of glucose into adipocytes and skeletal muscle).[8]

- Rosiglitazone binds to PPAR-γ with high affinity [dissociation constant (K_d) approximately 40 nmol/L].[6] It has a higher affinity for PPAR-γ in intact human adipocytes (IC_{50} 10 nmol/L) than pioglitazone (360 nmol/L) or troglitazone (1050 nmol/L).[9]

- Exposure of pluripotent C3H10T1/2 stem cells[6] or human preadipocytes[10] to rosiglitazone at concentrations as low as 100 nmol/L *in vitro* promoted their differentiation to adipocytes.[6] PPAR-γ expression in C3H10T1/2 cells was increased 3-fold.[6]

- Rosiglitazone inhibited leptin gene expression in rat 3T3-L1 adipocytes *in vitro*,[11,12] with an ED_{50} (concentration causing 50% inhibition) of 5 to 50 nmol/L, similar to its Kd for binding to PPAR-γ (40 nmol/L) and identical to its ED_{50} for inducing adipocyte differentiation (5 to 50 nmol/L).[12]

- In *in vivo* studies in obese or high-fat-diet-fed rats, rosiglitazone reduced *ob* mRNA levels in epididymal fat pads (by 40% at 5 mg/kg/day)[11] and reduced plasma leptin levels (≈40%; $p < 0.05$).[13,14] Expression of PPAR-γ and aP2 mRNA were significantly increased ($p < 0.01$).[13]

- Lipoprotein lipase mRNA and activity in epididymal adipose tissue increased by more than 2-fold after administration of rosiglitazone 5 or 10 mg/kg for 7 days to normal rats. A similar increase in mRNA levels was seen when the drug (10 μmol/L) was added to adipocytes *in vitro*.[15]

- Rosiglitazone enhanced expression of uncoupling proteins 1[16,17] and 3[17] (UCP-1 and UCP-3) [by 5- and 3-fold, respectively, at a concentration of 1 μmol/L[17]] in rat or human adipocytes *in vitro*.

Synergistic effects on UCP-3 were noted between rosiglitazone and the PPAR-α agonist Wy 14643,[17] which antagonised the effects of rosiglitazone on UCP-1.[18] Rosiglitazone also increased expression of UCP-2 in adipocytes.[19]

• Insulin binding to white adipocytes from obese mice was significantly ($p < 0.001$) increased by pretreatment with rosiglitazone (30 μmol/kg of diet for 14 days). The drug appeared to increase the number of insulin receptors rather than change receptor affinity and increased the total tissue content of GLUT-4 by 2.5-fold.[20]

Effects on Glucose and Lipid Metabolism

• In genetic and dietary animal models of obesity and insulin resistance, including the obese hyperglycaemic *db/db* mouse,[7,21,22] *ob/ob* mouse,[20,21] Zucker fatty (*fa/fa*) rat[23-27] and overfed Wistar rat,[5,14] rosiglitazone significantly reduces plasma levels of glucose, insulin and/or triglycerides. Rosiglitazone also lowered plasma levels of non-esterified fatty acids[5,23,28] and ketone bodies.[5]

• As with other thiazolidinediones,[8] the *in vivo* antidiabetic potency of rosiglitazone was correlated with its binding affinity for PPAR-γ.[7]

• Rosiglitazone had a greater effect on plasma triglycerides than on plasma glucose in Zucker fatty rats, improving dyslipidaemia at a dosage (10 to 30 mg/kg/day) which did not significantly lower plasma glucose levels.[27] In normal rats, rosiglitazone decreased serum triglycerides without affecting plasma glucose levels.[15]

• As with other thiazolidinediones,[8] rosiglitazone frequently increases food intake and promotes bodyweight gain and/or fat deposition in rodents.[11,14,15,25,29] However, no significant effect of thiazolidinediones on body fat mass has been reported in humans to date.[16] Specifically, thiazolidinediones increase the amount of brown adipose tissue (which dissipates energy via oxidation of fatty acids),[8] which might contribute to the effects of these drugs on insulin resistance.[16] Rosiglitazone enhanced rat interscapular brown adipose tissue mass.[30]

• Glucose tolerance in *ob/ob* mice was improved by rosiglitazone; at 100 μmol/kg of diet, the rise in blood glucose levels following an oral glucose load was completely abolished.[20] When given to young Zucker fatty rats (aged 6 weeks), rosiglitazone (≈10 μmol/kg) prevented development of hyperglycaemia, maintaining blood glucose levels similar to those in lean rats.[31]

• Under euglycaemic clamp conditions, rosiglitazone (10 μmol/kg/day for 4 days) increased glucose uptake, insulin suppressibility of hepatic glucose production and muscle glucose uptake; however, these effects were seen only in insulin-resistant rats.[5]

• Prior administration of rosiglitazone 3 mg/kg/day for 7 days to obese Zucker rats restored basal glucose uptake in the isolated perfused heart (from 42 to 15% lower than in lean control hearts).[23]

• Prior administration of rosiglitazone 3 μmol/kg/day to obese Zucker rats decreased the insulin resistance of perfused hindlimbs, as shown by increased responsiveness to insulin. However, no further details of results were provided.[32]

Effects on Diabetic Complications

• Administration of rosiglitazone (50 μmol/kg of diet) to Zucker rats protected against development and progression of renal injury and adaptive changes to pancreatic islet morphology which result from sustained hyperinsulinaemia. When given as a preventative strategy to young rats (aged 6 to 7 weeks) for 9 months, rosiglitazone delayed the onset (from 3 to 6 months), and markedly reduced subsequent progression, of proteinuria compared with untreated rats. Delayed progression of proteinuria was also noted when rosiglitazone was administered to older rats (age 24 to 25 weeks) with established proteinuria (intervention group). Normalisation of urinary *N*-acetyl-β-D-glucosaminidase activity (a marker for renal proximal tubular damage) and attenuation of the rise in systolic blood pressure that accompanied the development of proteinuria was noted in both groups of rats. Postmortem, histological and ultrastructural examination confirmed the renal protective effect of the drug:

nephromegaly and signs of chronic nephropathy seen in control animals were attenuated or prevented in the prevention group and attenuated in the intervention group. Similarly, pancreatic islet hyperplasia and other pancreatic abnormalities were prevented or attenuated.[25]

• Rosiglitazone (30 μmol/kg of diet for 10 days) significantly increased the area, number and insulin content of pancreatic islets in *db/db* mice, possibly reflecting reduced secretory pressure on the β-cell after normalisation of hyperglycaemia. Insulin and amylin gene expression were unchanged in this model.[22] However, in another study hyperexpression of these genes in Zucker fatty rats was reduced (≈50%) by rosiglitazone administration (3 μmol/kg/day for 21 days).[33]

• Rosiglitazone (50 μmol/kg of diet) protected against impaired endothelial function when given to young Zucker rats for 9 to 12 weeks. Vasorelaxant responses of isolated mesenteric resistance vessels to insulin and acetylcholine were partially preserved.[24]

2. Pharmacokinetics and Drug Interactions

• Administration of rosiglitazone with food reduced the rate, but not the extent, of absorption of the drug. A crossover study in 12 healthy volunteers found that area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) after administration of rosiglitazone 2mg was similar in the fasted and fed state (860 versus 805 μg/L · h), but mean maximum plasma concentration (C_{max}) was reduced by 20% (from 152 to 121 μg/L) and time to C_{max} (t_{max}) was delayed by 2.2 hours (1.3 *vs* 3.5 hours), by food intake. Elimination half-life ($t_{½β}$) was 3.64 versus 3.78 hours.[34]

• Comparison of pharmacokinetics in young (aged 18 to 45 years) and elderly (aged ≥65 years) healthy volunteers after a single 4mg dose of rosiglitazone showed that $AUC_{0-\infty}$ and C_{max} were 36 and 38% lower in the older group. However, $t_{½}$ and t_{max} were similar in the 2 age groups.[35]

• The pharmacokinetics of rosiglitazone were unaltered by mild to moderate renal impairment[36] or end-stage renal failure with haemodialysis.[37] The unbound drug fraction was almost 40% higher in patients with severe renal impairment;[36] nevertheless, adjustment of rosiglitazone dosage is not necessary on the basis of impaired renal function.[36,37]

• However, dosage reduction is required in patients with impaired hepatic function: total and unbound AUC were increased by approximately one-third and 3-fold, respectively and $t_{½β}$ by approximately 1.5-fold (6.0 *vs* 3.8 hours) compared with healthy volunteers.[38]

• In contrast with troglitazone,[39] rosiglitazone does not appear to induce cytochrome P450 (CYP) 3A4 metabolism. Concomitant administration of rosiglitazone (8 mg/day for 14 days) did not affect the pharmacokinetics of the CYP3A4 substrates nifedipine[40] or ethinylestradiol or norethindrone (in a combined oral contraceptive formulation).[41]

• Similarly, rosiglitazone did not interact with ranitidine,[42] metformin[43] or digoxin.[44]

• Administration of acarbose (100mg 3 times daily for 7 days) slightly reduced absorption (AUC; 12%) of a single 8mg dose of rosiglitazone and prolonged $t_{½}$ by approximately 1 hour. However, this was not considered clinically relevant.[45]

3. Therapeutic Trials

Rosiglitazone has been evaluated in clinical trials in patients with type 2 diabetes. Generally, patients had previously been managed with diet or other antidiabetic agents and treatment with rosiglitazone was preceded by a placebo or no-treatment run-in period of 3 to 8 weeks. Mean baseline fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA_{1c}) were >10.2 mmol/L and >8%, respectively, in all studies. Changes in HbA_{1c} are expressed as absolute reductions or increases from baseline or placebo.

Dose-Ranging Studies

• A 12-week double-blind multicentre study compared rosiglitazone 0.05, 0.25, 1 or 2mg twice daily

with placebo in 380 patients. The 1 and 2mg twice daily dosages were effective in reducing FPG; ($p = 0.001$) and fructosamine ($p = 0.003$ for 2mg twice daily group) from baseline, but HbA_{1c} was not significantly reduced in any of the treatment groups. The higher dosage also reduced plasma insulin (by 2.7 mIU/L; $p = 0.0044$) and free fatty acid ($p = 0.0014$) levels and increased total, high density lipoprotein (HDL)- and low density lipoprotein (LDL)-cholesterol ($p < 0.001$).[46]

• Once daily treatment with rosiglitazone 4, 8 or 12 mg/day for 8 weeks significantly reduced FPG, by 0.8, 2.0 and 1.7 mmol/L (15.8, 35.7 and 30.2 mg/dl), respectively ($p < 0.0001$ for all doses). FPG increased by 0.4 mmol/L (7.4 mg/dl) in placebo recipients in this randomised double-blind study in 369 patients. 8 mg/day was more effective than 4 mg/day, but no additional antihyperglycaemic effect was seen with 12 mg/day (fig. 1). Over 50% of patients treated with the 2 highest dosages had an FPG reduction of >1.7 mmol/L (>30 mg/dl).[47]

• A randomised placebo-controlled study compared rosiglitazone 4 and 8 mg/day, given as a single daily dose or in 2 divided daily doses, in 959 patients (treatment duration not stated). HbA_{1c} and FPG decreased significantly without any increase in serum insulin levels in all active treatment groups. Compared with placebo, HbA_{1c} decreased by 0.8, 0.9, 1.1 and 1.5% in the rosiglitazone 4mg once daily, 2mg twice daily, 8mg once daily and 4 mg twice daily treatment groups ($p < 0.0001$ all comparisons).[48]

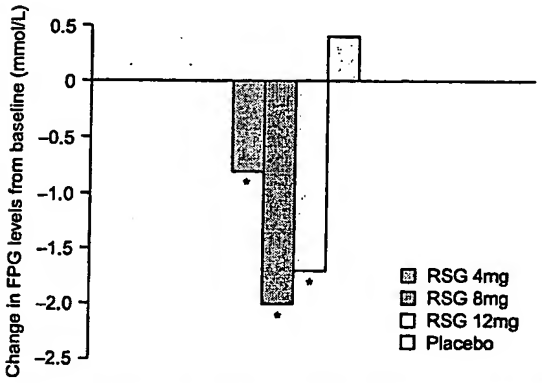


Fig. 1. Antihyperglycaemic efficacy of once daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels after receiving RSG 4, 8 or 12mg once daily or placebo for 8 weeks in a randomised double-blind study in 369 patients with type 2 diabetes mellitus.[47] * $p < 0.0001$

• In a multicentre, placebo-controlled 26-week study in 493 patients, rosiglitazone 2 or 4mg twice daily reduced FPG and HbA_{1c} by 2.1 and 3 mmol/L (38.4 and 54.0 mg/dl) and 0.28 and 0.56%, respectively, from baseline ($p < 0.0001$ *vs* placebo). These parameters increased by 1.0 mmol/L (18.9 mg/dl) and 0.92% in placebo recipients (fig. 2). Serum fructosamine was also significantly reduced by both dosages of rosiglitazone ($p < 0.0001$ *vs* placebo).[49]

• In a study in 99 patients, treatment with rosiglitazone 2, 4 or 6mg twice daily for 8 weeks significantly decreased the postprandial plasma glucose AUC (by 144.4, 177.1 and 175.0 mg/dl · h, respectively) and plasma insulin AUC (by 34.0, 77.8 and 139.9 pmol/L · h, respectively) [$p < 0.0004$ *vs* baseline and placebo for all treatment groups].[50]

• Rosiglitazone appeared to be equally effective in older (aged ≥65 years) and younger (<65 years) patients. In two 26-week placebo-controlled studies, rosiglitazone 4 and 8 mg/day achieved similar reductions in FPG and HbA_{1c} in the 2 age groups.[51]

Comparison with Glibenclamide

• Rosiglitazone 4mg twice daily was more effective ($p = 0.033$), and rosiglitazone 2mg twice daily was slightly less effective, than optimally titrated glibenclamide (glyburide) in producing sustained reductions in FPG over a 12-month period. 587 patients participated in this randomised, double-blind study. FPG was reduced by 1.4, 2.3 and 1.7 mmol/L (25, 41 and 30 mg/dl) with rosiglitazone 4 mg/day, rosiglitazone 8 mg/day and glibenclamide, respectively, and 36, 51 and 37% of patients had levels <7.8 mmol/L (140 mg/dl) after treatment. Rosiglitazone 8 mg/day was slightly, but not significantly, less effective than glibenclamide in reducing HbA_{1c} (by 0.53 *vs* 0.72%).[52]

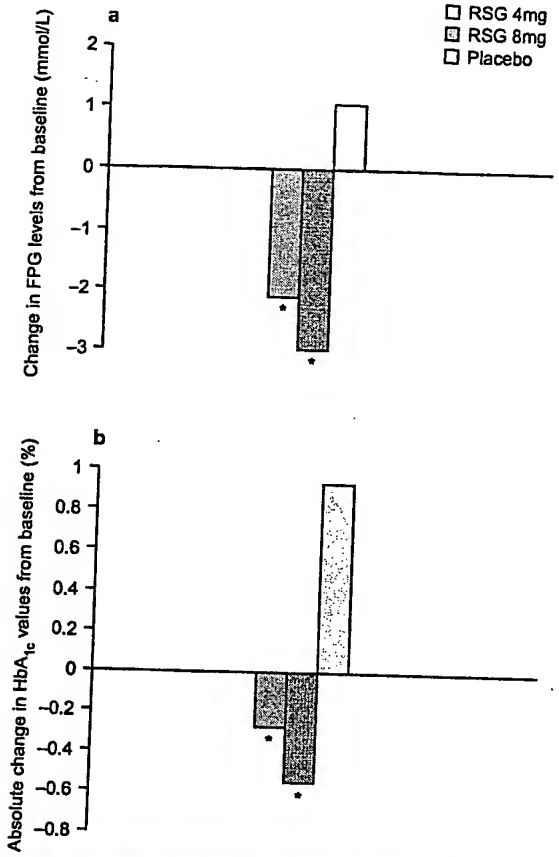


Fig. 2. Antihyperglycaemic efficacy of twice daily rosiglitazone (RSG). Fasting plasma glucose (FPG) levels (a) and glycosylated haemoglobin (HbA_{1c}) (b) after receiving RSG 2 or 4mg twice daily or placebo in a multicentre 26-week study in 493 patients with type 2 diabetes mellitus.[49] * $p < 0.0001$.

Use in Combination with Other Agents

Studies evaluating rosiglitazone as combination treatment with sulphonylureas, metformin or insulin were all randomised and placebo-controlled.

- Addition of rosiglitazone 2 or 4 mg/day (in 2 divided daily doses) to existing sulphonylurea therapy (gliclazide, glibenclamide glipizide) for 6 months produced additional reductions in HbA_{1c} (0.6 and 1.0%; $p < 0.0001$) and FPG (1.3 and 2.4 mmol/L; 24.3 and 43.9 mg/dl). Worsening of these parameters occurred in placebo recipients. 574 patients participated in this double-blind study. Over half of patients treated with the higher dosage of rosiglitazone achieved a reduction of ≥0.7% in HbA_{1c} and ≥1.7 mmol/L (30 mg/dl) in FPG. Free fatty acids decreased by approximately 15% and HDL- and LDL-cholesterol increased by 10 and 5%, respectively, in this treatment group.[53]

- In patients (n = 348) poorly controlled by maximal metformin therapy (2.5 g/day), addition of rosiglitazone 4 or 8 mg/day (once daily) for 26 weeks improved glycaemic control without changing serum insulin levels. FPG decreased by 2.2 and 2.9 mmol/L (39.8 and 52.9 mg/dl) and HbA_{1c} by 0.97 and 1.18%, respectively ($p < 0.0001$ all comparisons). FPG levels <7.8 mmol/L (140 mg/dl) were achieved in 22 and 30% of patients, respectively, despite mean baseline levels of >11.7 mmol/L (210 mg/dl).[54]

- In patients (n = 319) poorly controlled on twice daily insulin, addition of rosiglitazone 2 or 4mg twice daily significantly improved glycaemic control and lowered insulin requirements (by 4.8 and 9.4 U/day, respectively; $p < 0.006$ both comparisons) [fig. 3]. Over the 26-week study period, FPG was reduced by 2.3 and 2.5 mmol/L (41.5 and 44.4 mg/dl) from baseline with rosiglitazone 4 and 8 mg/day, respectively, but increased by 0.6 mmol/L (10.3 mg/dl) in placebo recipients. HbA_{1c} was decreased by 0.6 and 1.2% compared with an increase of 0.1% in the placebo group. Over half of patients receiving the higher dose of rosiglitazone had a decrease of ≥1% in HbA_{1c}.[55]

Homeostasis Model Assessment

- Treatment with rosiglitazone 2 to 8 mg/day with or without sulphonylureas or metformin for 26 weeks decreased insulin resistance (≈3 to 25%) and improved β-cell function (≤94%), according to a homeostasis model assessment (HOMA).[56] Insulin resistance increased in those who received placebo or sulphonylurea monotherapy and did not improve in those treated with metformin (fig. 4).[57,58]

4. Tolerability

• Analysis of pooled data from 4327 patients treated with rosiglitazone, alone or in combination with metformin or sulphonylureas, showed that the only adverse events reported in ≥5% of patients receiving rosiglitazone were upper respiratory tract infection (13.1% of monotherapy recipients), injury (8.9%) and headache (6.7%). The relationship of these events to treatment was not stated. Adverse events related to the cardiovascular system, elevated serum lipids, anaemia or oedema were at least as common with placebo as with rosiglitazone.[59] Overall, fewer rosiglitazone than placebo recipients withdrew from clinical trials because of adverse events (≤6.2 to 7.8% *vs* 10.8%).[48,59]

• According to an analysis of 2526 rosiglitazone-treated patients, the proportions of patients with at least 1 adverse event did not differ between elderly (aged ≥65 years) and younger patients. As with younger patients, the most common events in the elderly were upper respiratory tract infection, injury and headache and these were equally common in the 2 age groups. However, oedema and anaemia appeared to be more common in the elderly (7.5 *vs* 3.5% and 2.5 *vs* 1.7%).[51]

• Coadministration of rosiglitazone did not increase the frequency of hypoglycaemia associated with sulphonylureas or increased plasma lactate levels or gastrointestinal events associated with metformin.[59]

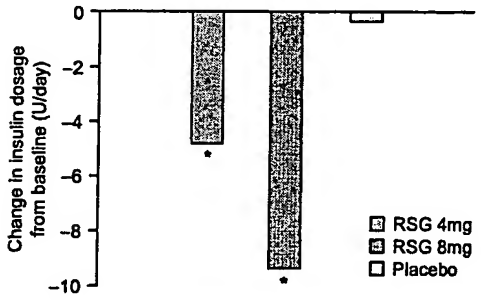


Fig. 3. Efficacy of rosiglitazone (RSG) in combination with insulin. Effects on insulin requirements of adding RSG 2 or 4mg twice daily or placebo to existing twice daily insulin therapy in patients (n = 319) with poorly controlled type 2 diabetes mellitus who participated in a randomised study.[55] * $p < 0.006$.

Hypoglycaemia

• Hypoglycaemia occurred in <1% of 2526 patients receiving rosiglitazone (dosage not stated) in clinical trials.[51] In a comparative study, hypoglycaemia was more common with glibenclamide (optimally titrated; 12% of 203 patients) than with rosiglitazone 4 or 8 mg/day (<2% of 384 patients).[52]

• Rosiglitazone did not appear to increase the risk of hypoglycaemia associated with moderate alcohol intake (0.6 g/kg) with a meal. Concomitant intake of alcohol did not produce any clinically meaningful changes in plasma glucose or overnight urinary cortisol : creatinine ratios in patients who received rosiglitazone 8 mg/day (n = 11) or placebo (n = 12) for 8 weeks. Hypoglycaemia did not occur.[60]

Effects on the Liver

Troglitazone has been found to cause significant hepatic toxicity, which has resulted in death or the need for liver transplantation in a small number of patients.[39] Thus, concern has been raised as to whether this is a class effect of thiazolidinediones. To date, there is no evidence that rosiglitazone is hepatotoxic.

• Pooled data are available from >4500 patients treated with rosiglitazone for ≥6 months in double-blind or open-label studies. Of 3455 patients who had frequent liver function tests (every 4 weeks for the first 3 months, every 6 weeks for the next 3 months and quarterly thereafter) in double-blind controlled studies, the proportion of patients with serum ALT levels >3 times the upper limit of normal (>3 × ULN; 0.17%; n = 6) was similar to that in patients receiving placebo (0.18%; n = 1 of 561) or sulphonylureas or metformin (0.48%; 4/828). [Patients with baseline ALT or AST values ≤2.5 × ULN were allowed to enter the studies.] Of 13 patients who developed ALT levels >3 × ULN during rosiglitazone treatment (during controlled clinical

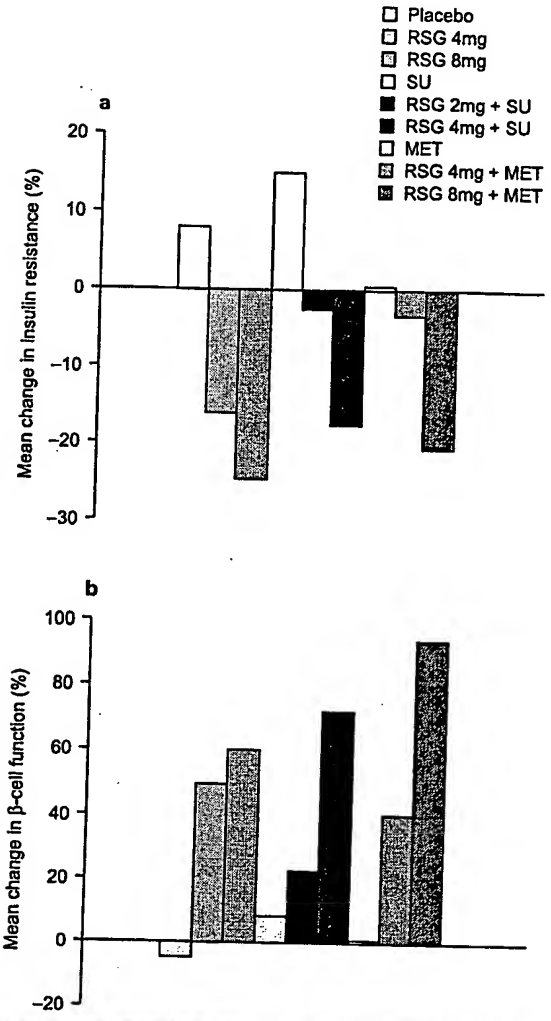


Fig. 4. Effects of rosiglitazone (RSG) and other antidiabetic agents on insulin resistance (a) and β-cell function (b) in a homeostasis model assessment. Patients participating in 3 clinical trials received placebo (n = 158), RSG 2mg twice daily (n = 166), RSG 4mg twice daily (n = 169), sulphonylurea therapy (SU; n = 192), RSG 1mg twice daily + SU (n = 199), RSG 2mg twice daily + SU (n = 183), metformin (MET; n = 113), RSG 4mg once daily + MET (n = 116), RSG 8mg once daily + MET (n = 110) for 26 weeks.[57,58]

trials or open-label treatment), levels either improved, normalised or did not worsen during continued therapy (follow-up data were not available for 2 patients).[61]

• These data are supported by the results of a study in rat hepatocytes. In contrast to troglitazone, which was toxic to these cells at a concentration of 20 μmol/L, rosiglitazone showed no cytotoxicity at concentrations ≤100 μmol/L.[62]

Effects on the Cardiovascular System

• As with other thiazolidinediones, rosiglitazone has been associated with small and/or clinically insignificant decreases in haematocrit and haemoglobin in patients with type 2 diabetes.[46,49] Rosiglitazone 4 or 8 mg/day for 8 weeks did not affect indices of erythropoiesis or red blood cell destruction in healthy volunteers (n = 30). Haemoglobin and haematocrit were reduced slightly (0.6 g/L and 2%, respectively) in the 8mg dosage group, presumably as a result of increased plasma volume.[63]

• Cardiac hypertrophy has been noted in rodents given high doses of thiazolidinediones. However, treatment of 104 patients with rosiglitazone 4mg twice daily for up to 52 weeks did not result in any adverse changes in cardiac structure or function, on the basis of echocardiographic studies. Only small and clinically unimportant changes were seen in left ventricular mass index and left ventricular end diastolic volume. Ejection fraction was unchanged. Similar results were seen in patients treated with glibenclamide (mean 10.5 mg/day) over the same time period. Diastolic blood pressure was lowered by 2.3mm Hg ($p = 0.0016$) in rosiglitazone recipients, as assessed by 24-hour ambulatory monitoring.[64]

• Similarly, no changes in left ventricular mass were detected on echocardiography in 380 patients treated with rosiglitazone 0.1 to 4 mg/day or placebo for up to 12 weeks.[65]

• Thiazolidinediones can cause oedema and haemodilution, and animal studies have shown that troglitazone has a vasodilatory effect which might lead to fluid retention. However, an *in vitro* study in human resistance vessels showed that rosiglitazone did not have the direct vasorelaxant effect noted with troglitazone. Troglitazone also had a similar vasodilatory effect in Wistar rat arteries that was not abolished by N^G-nitro-L-arginine methyl ester.

Further studies are required to determine whether these differences are apparent *in vivo*.[66]

5. Rosiglitazone: Current Status

Rosiglitazone is a thiazolidinedione insulin sensitiser that has been filed for approval for the management of type 2 diabetes mellitus.

References

1. Whitcomb RW, Saltiel AR. Thiazolidinediones. Expert Opin Invest Drug 1995; 4 (12): 1299-309
2. Henry RR. Type 2 diabetes care: the role of insulin-sensitizing agents and practical implications for cardiovascular disease prevention. Am J Med 1998 Jul 6; 105 Suppl. 1A: 20S-6S
3. Bloomgarden ZT. Insulin resistance: current concepts. Clin Ther 1998 Mar-Apr; 20: 216-31
4. Grossman SL, Lessem J. Mechanisms and clinical effects of thiazolidinediones. Expert Opin Invest Drug 1997; 6 (8): 1025-40
5. Oakes ND, Kennedy CJ, Jenkins AB, et al. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. Diabetes 1994 Oct; 43: 1203-10
6. Lehmann JM, Moore LB, Smith-Oliver TA, et al. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPAR γ). J Biol Chem 1995; 270 (22): 12953-6
7. Berger J, Bailey P, Biswas C, et al. Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-τ: binding and activation correlate with antidiabetic actions in db/db mice. Endocrinology 1996 Oct; 137: 4189-95
8. Spiegelman BM. PPAR-γ: Adipogenic regulator and thiazolidinedione receptor. Diabetes 1998; 47 (4): 507-14
9. Young PW, Buckle DR, Cantello BCC, et al. Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor γ. J Pharmacol Exp Ther 1998 Feb; 284: 751-9
10. Prins J, Adams M, Holder J, et al. Thiazolidinediones promote human pre-adipocyte differentiation and activate hPPAR-γ [abstract]. J Endocrinol 1996 Mar; 148 Suppl.: P53
11. De-Vos P, Lefebvre A-M, Miller SG, et al. Thiazolidinediones repress *ob* gene expression in rodents via activation of peroxisome proliferator-activated receptor γ. J Clin Invest 1996 Aug 15; 98: 1004-9
12. Kallen CB, Lazar MA. Antidiabetic thiazolidinediones inhibit leptin (*ob*) gene expression in 3T3-L1 adipocytes. Proc Natl Acad Sci U S A 1996 Jun 11; 93: 5793-6
13. Pearson SL, Cawthorne MA, Clapham JC, et al. The thiazolidinedione insulin sensitiser, BRL 49653, increases the expression of PPAR-γ and aPd2 in adipose tissue of high-fat-fed rats. Biochem Biophys Res Commun 1996 Dec 24; 229: 752-7
14. Pickavance L, Tadayyon M, Widdowson P. Therapeutic index for rosiglitazone in dietary obese rats and effects on body weight and plasma leptin [abstract]. Diabetic Med 1998; 15 Suppl. 2: S28
15. Lefebvre A-M, Peinado-Onsurbe J, Leitersdorf I, et al. Regulation of lipoprotein metabolism by thiazolidinediones occurs through a distinct but complementary mechanism relative to fibrates. Arterioscler Thromb Vasc Biol 1997 Sep; 17: 1756-64
16. Digby JE, Montague CT, Sewter CP, et al. Thiazolidinedione exposure increases the expression of uncoupling protein 1 in cultured human preadipocytes. Diabetes 1998 Jan; 47: 138-41
17. Teruel T, Smith S, Clapham J. Rosiglitazone and Wy 14643 act synergistically to enhance UCP-3 expression in brown adipocytes. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
18. Teruel T, Smith S. Differential regulation of UCP-1 expression by rosiglitazone and Wy 14643 in brown adipocytes [abstract]. Diabetes 1998 May; 47 Suppl. 1: A17
19. Aubert J, Champigny O, Saint-Marc P, et al. Up-regulation of UCP-2 gene expression by PPAR agonists in preadipose and adipose cells. Biochem Biophys Res Commun 1997 Sep 18; 238: 606-11
20. Young PW, Cawthorne MA, Coyle PJ, et al. Repeat treatment of obese mice with BRL 49653, a new and potent insulin sensitizer, enhances insulin action in white adipocytes: association with increased insulin binding and cell-surface GLUT4 as measured by photoaffinity labeling. Diabetes 1995 Sep; 44: 1087-92
21. Lohray BB, Bhushan V, Rao BP, et al. Novel euglycemic and hypolipidemic agents: 1. J Med Chem 1998 May 7; 41: 1619-30
22. Lister CA, Boam D, Bretherton-Watt D, et al. Rosiglitazone increases pancreatic islet area, number and insulin content, but not insulin gene expression [abstract]. Diabetologia 1998 Aug; 41 Suppl. 1: A169
23. Draper N, Clarke K, Buckingham R, et al. Rosiglitazone restores basal glucose uptake in the obese Zucker rat heart. Abstract accepted for American Diabetic Association Meeting; 1999 Jun 19-22, San Diego
24. Walker A, Chattington P, Buckingham R, et al. BRL 49653, a new insulin-sensitizing agent, protects against impairment of endothelial function in Zucker fatty rats [abstract]. Diabetes 1996 May; 45 Suppl. 2: 222A
25. Buckingham RE, Al-Barazanji KA, Toseland CDN, et al. Peroxisome proliferator-activated receptor-τ agonist, rosiglitazone, protects against nephropathy and pancreatic islet abnormalities in Zucker fatty rats. Diabetes 1998 Aug; 47: 1326-34
26. Finegood DT, McArthur MD, Dunichand-Hoedl A, et al. The PPAR-γ agonist, rosiglitazone, reverses hyperinsulinemia and promotes growth of islet beta-cell mass [abstract]. Diabetes 1998 May; 47 Suppl. 1: 47
27. Oliver Jr W, Boncek V, Wiard R, et al. Responders and nonresponders: treatment with the thiazolidinedione insulin sensitizer, BRL 49653, improves diabetic dyslipidemia more than reducing hyperglycemia in ZDF rats [abstract]. Diabetes 1996 May; 45 Suppl. 2: 316A
28. Oakes ND, Camilleri S, Furler SM, et al. The insulin sensitizer, BRL 49653, reduces systemic fatty acid supply and utilization and tissue lipid availability in the rat. Metabolism 1997 Aug; 46: 935-42
29. Wang Q, Dryden S, Frankish HM, et al. Increased feeding in fatty Zucker rats by the thiazolidinedione BRL 49653 (rosiglitazone) and the possible involvement of leptin and hypothalamic neuropeptide Y. Br J Pharmacol 1997 Dec; 122: 1405-10
30. Tai TAC, Jennermann C, Brown KK, et al. Activation of the nuclear receptor peroxisome proliferator-activated receptor γ promotes brown adipocyte differentiation. J Biol Chem 1996 Nov 22; 271: 29909-14
31. Smith SA, Lister CA, Hughes MG, et al. The PPAR-γ agonist, BRL 49653, prevents progression to diabetes in Zucker diabetic fatty rats [abstract]. Diabetologia 1997 Jun; 40 Suppl. 1: A46
32. Eldershaw TPD, Rattigan S, Cawthorne MA, et al. Prior treatment of obese Zucker rats with the thiazolidinedione (BRL

49653) decreases insulin resistance in perfused hindlimb [abstract]. Diabetes Care 1995 Jun; 18 Suppl. 2: A16
33. Smith S, Boam D, Cawthorne MA, et al. Rosiglitazone improves insulin sensitivity and reduces hyperexpression of insulin and amylin mRNA's in pancreatic islets [abstract]. Diabetes 1998 May; 47 Suppl. 1: A94
34. Freed MI, Jorkasky DK, DiCicco RA. The bioavailability of rosiglitazone is unaltered by food. Eur J Clin Pharmacol. In press
35. DiCicco R, Freed M, Allen A, et al. A study of the effect of age on the pharmacokinetics of BRL 49653C in healthy volunteers [abstract]. J Clin Pharmacol 1995 Sep; 35: 926
36. Chapelsky MC, Thompson K, Miller A. Effect of renal impairment on the pharmacokinetics of rosiglitazone (RSG). Clin Pharmacol Ther 1999; 65 (2): 185
37. Thompson K, Zussman B, Miller A. Pharmacokinetics of rosiglitazone are unaltered in hemodialysis patients [abstract]. Clin Pharmacol Ther 1999 Feb; 65 (2): 186
38. Miller AK, Inglis AL, Thompson K. Effect of hepatic impairment on the pharmacokinetics (PK) of rosiglitazone (RSG) [abstract]. Clin Pharmacol Ther 1999 Feb: 186
39. Plosker GL, Faulds D. Troglitazone: a review of its use in the management of type 2 diabetes mellitus. Drugs 1999; 57 (3): 409-38
40. Freed MI, Miller A, Inglis AM, et al. Rosiglitazone, a PPAR-γ agonist, does not alter the pharmacokinetics of nifedipine, a cytochrome P450 3A4-substrate [abstract]. Diabetes 1998 May; 47 Suppl. 1: A94
41. Inglis AM, Miller AK, Culkin KT, et al. Rosiglitazone, a PPAR agonist, does not alter the pharmacokinetics of oral contraceptives (OC). Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
42. Freed MI, Miller A, Jorkasky DK, et al. Rosiglitazone pharmacokinetics are not affected by coadministration of ranitidine [abstract]. Diabetes 1998 May; 47 Suppl. 1: A353
43. DiCicco R, Allen A, Jorkasky D, et al. Lack of pharmacokinetic drug interaction between rosiglitazone (BRL 49653C) and metformin [abstract]. Clin Pharmacol Ther 1998 Feb; 63: 155
44. Dicicco RA, Allen A, Jorkasky DK, et al. Chronic administration of rosiglitazone does not alter the pharmacokinetics of digoxin [abstract]. Diabetes 1998 May; 47 Suppl. 1: A353
45. Inglis AML, Miller AK, Thompson KA, et al. Coadministration of rosiglitazone and acarbose (A): lack of a clinically relevant pharmacokinetic drug interaction [abstract]. Diabetes 1998 May; 47 Suppl. 1: A353
46. Patel J, Anderson RJ, Rappaport EB. Rosiglitazone monotherapy improves glycemic control in patients with type 2 diabetes: a 12-week, randomized, placebo-controlled study. Diabetes Obesity Metab. In press
47. Nolan JJ, Jones NP, Patwardhan R, et al. Once-daily rosiglitazone is effective in the treatment of type 2 diabetes mellitus. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
48. Grunberger G, Weston WM, Patwardhan R, et al. Rosiglitazone once or twice daily improves glycemic control in patients with type 2 diabetes. Poster accepted for American Diabetic Association Meeting; 1999 Jun 19-22, San Diego
49. Patel J, Miller E, Patwardhan R. Rosiglitazone improves glycaemic control when used as a monotherapy in type 2 diabetic patients [abstract]. Diabetic Med 1998; 15 Suppl. 2: S37-8
50. Raskin P, Rappaport EB. Rosiglitazone (RSG) improves fasting and postprandial plasma glucose in type 2 diabetes. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
51. Beebe KL, Patel J. Rosiglitazone is effective and well tolerated in patients ≥65 years with type 2 diabetes. Poster accepted for American Diabetic Association Meeting; 1999 Jun 19-22; San Diego
52. Charbonnel B, Lönnqvist F, Jones NP, et al. Rosiglitazone is superior to glyburide in reducing fasting plasma glucose after 1 year of treatment in type 2 diabetes patients. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
53. Gomis R, Jones NP, Vallance SE, et al. Low-dose rosiglitazone (RSG) provides additional glycemic control when combined with sulfonylureas in type 2 diabetes (T2D). Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
54. Fonseca V, Biswas N, Salzman A. Once-daily rosiglitazone (RSG) in combination with metformin (MET) effectively reduces hyperglycemia in patients with type 2 diabetes. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
55. Raskin P, Dole JF, Rappaport EB. Rosiglitazone improves glycemic control in poorly controlled, insulin-treated type 2 diabetes. Poster accepted for American Diabetes Association Meeting 1999, Jun 19-22, San Diego
56. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9
57. Patel J, Weston WM, Hemyari P. Rosiglitazone (RSG) decreases insulin resistance (IR) and improves beta-cell function (BCF) in patients with type 2 diabetes mellitus (T2DM). SmithKline Beecham; data on file
58. Data on file, SmithKline Beecham.
59. Kreider M, Miller E, Patel J. Rosiglitazone is safe and well tolerated as monotherapy or combination therapy in patients with type 2 diabetes mellitus. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
60. Culkin KT, Patterson SD, Jorkasky DK, et al. Rosiglitazone (RSG) does not increase the risk of alcohol-induced hypoglycemia in diet-treated type 2 diabetics. Abstract accepted for American Diabetic Association Meeting; 1999 Jun 19-22, San Diego
61. Salzman A, Patel J. Rosiglitazone is not associated with hepatotoxicity. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
62. Elcock FJ, Lyon JJ, Hitchcock J, et al. Toxicity of troglitazone in cultured rat hepatocytes. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
63. Dogterom P, Jonkman JHG, Vallance SE. Rosiglitazone: no effect on erythropoiesis or premature red cell destruction. SmithKline Beecham; data on file
64. St John Sutton M, Dole J, Rappaport EB. Rosiglitazone does not adversely affect cardiac structure or function in patients with type 2 diabetes. Poster accepted for American Diabetes Association Meeting; 1999 Jun 19-22, San Diego
65. Miller E, Patel J, Reichek N, et al. BRL 49653 (a thiazolidinedione) is well tolerated and has no effect on LV mass following 12 weeks treatment in NIDDM patients [abstract]. Diabetes 1997 May; 46 Suppl. 1: 96A
66. Walker AB, Naderali EK, Chattington PD, et al. Differential vasoactive effects of the insulin sensitizers rosiglitazone (BRL 49653) and troglitazone on human small arteries *in vitro*. Diabetes 1998 May; 47: 810-4

Correspondence: *Julia A. Barman Balfour*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz